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Unconsciousness and sedation as precipitating factors of diabetic ketoacidosis

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ABSTRACT

The aim of this study was to identify medico-legal situations characterized by increased vitreous glucose concentrations, potentially lethal blood 3-hydroxybutyrate levels and conditions that could either incapacitate or lead to death on their own. The above was investigated in order to verify whether prolonged states of unconsciousness may play a role in precipitating diabetic ketoacidosis. Six groups of medico-legal situations (corresponding to 206 autopsy cases) were identified. Among these, three cases were characterized by pathologically increased vitreous glucose and blood 3-hydroxybutyrate levels. In one case diabetic ketoacidosis coexisted with underlying features that might have potentially incapacitated or lead to death on their own, whereas in two cases it corresponded with potentially lethal or lethal drug concentrations. The results of this study highlight the usefulness of systematically performing biochemistry in order to identify diabetic ketoacidosis-related deaths, even when autopsy and toxicology results provide apparently conclusive findings.

1. Introduction

Diabetic ketoacidosis (DKA) is a potentially life-threatening complication of diabetes that typically affects patients with type 1 diabetes mellitus. DKA generally results from the combination of absolute or relative circulating insulin deficiency and increased counter-regulatory hormone levels. Absolute insulin deficiency usually occurs in previously undiagnosed cases of type 1 diabetes and when patients on treatment deliberately or inadvertently fail to take insulin. Relative insulin deficiency occurs when the concentrations of counter-regulatory hormones increase under considerably stressful conditions such as trauma, injury, surgery or sepsis. Nevertheless, relatively mild illnesses (including respiratory infections or gastro-intestinal upsets with diarrhea and vomiting) and even emotional turmoil can cause an enhanced release of counter-regulatory hormones, thereby disrupting metabolic homeostasis and glycemic control, with consequent ketoacidosis.[1]

It has long been known that patients with type 2 diabetes mellitus, particularly of prolonged duration, may develop DKA under stressful conditions. However, in recent years, an increasing number of ketoacidosis cases without precipitating causes have been reported in children and adults with type 2 diabetes.[2,3]

Infections and deliberate or inadvertent non-compliance with insulin treatment (omission of or inadequate insulin therapy, discontinuation of insulin use) are the most frequent factors potentially precipitating DKA. Other less frequent, facilitating factors include trauma and vascular incidents.[2–4]

Illicit drug use, notably cocaine, has been described as another possible precipitating factor for ketoacidosis in diabetic patients.

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This may not only be due to poor or non-compliance with insulin therapy, but to the effects of cocaine itself on counter-regulatory hormone release. Second-generation antipsychotics can also be responsible for glucose control disturbances by causing weight gain, worsening insulin sensitivity and primarily damaging pancreatic islet cells.[5–7]

If the importance of major stressful conditions in disrupting metabolic homeostasis has widely been described in the literature, disparagingly few reports have analyzed the role that sedation, incapacitation and prolonged loss of consciousness may play in glucose control disturbances. These losses of consciousness may result from head injury, massive gastro-intestinal bleeding, myocardial infarction or potentially lethal levels of psychotropic drugs and cause hyperglycemia and ketoacidosis in diabetics as a consequence of unintentional treatment omission.

Should targeted biochemical analyses fail to be performed, autopsy and toxicology can still theoretically reveal the cause of death in such cases, though diabetic ketoacidosis may actually have played a role as important as, if not more than, intracranial bleeding, myocardial infarction and intoxication in causing the terminal events.

The aim of this study was to identify medico-legal cases simultaneously characterized by conditions either incapacitating or leading to death on their own, considerably increased vitreous glucose concentrations and potentially lethal blood ketone levels. The goal of our investigations was to evaluate whether prolonged states of unconsciousness may play a role in causing or facilitating accidental non-compliance with medical treatment and ketoacidosis possibly responsible for the death.

2. Material and methods

2.1. Forensic autopsy cases

From 2007 to 2012, vitreous humor and cerebrospinal fluid samples were systematically collected from consecutive deceased subjects after their arrival at the morgue (1–48 h after death).

Medico-legal situations possibly causing either prolonged loss of consciousness or death included:

- head injury causing cerebral edema associated with intracranial bleeding and/or cerebral contusion,
- subarachnoid or intraparenchymal hemorrhage following cerebral aneurysm or vascular malformation rupture,
- massive gastro-intestinal bleeding,
- acute coronary artery thrombosis,
- acute myocardial infarction,
- high blood levels of psychotropic drugs, whether medically prescribed or illegally obtained.

Blood samples were also systematically taken from the same cases during autopsy (3–51 h after death), as well as pericardial fluid and urine samples when available. In total, 500 cases were included in this study (388 males and 112 females), with a mean age of 59.6 years. Samples from severely decomposed bodies were rejected as well as cases presenting severe cranial destruction and where vitreous humor was unavailable. Only cases with both vitreous humor and available blood samples (femoral or cardiac blood) were considered. All cases included in the study underwent complete autopsies preceded by unenhanced CT-scans and, in selected cases, postmortem angiographies. Histology, toxicology and biochemical investigations (vitreous glucose, sodium and chloride, postmortem serum urea and creatinine as well as blood and vitreous 3-hydroxybutyrate (3HB) levels) were performed in all cases. Microbiology and neuropathological investigations were carried out only in selected cases. Medical records and social histories of the deceased subjects as well as police reports were reviewed in all cases before conclusions were made. Diabetic and non-diabetic subjects were identified based on the medical records. All cases originated from forensic practice with most of deaths occurred outside the hospital. Data on antemortem biochemical results levels shortly before death were therefore unavailable. All autopsies were ordered by the public prosecutor due to unclear circumstances of death.

2.2. Sample collection

Undiluted vitreous humor samples (between 1 and 3 ml) were obtained by aspiration using a sterile needle and syringe. Right and left vitreous samples were collected through a scleral puncture at the lateral canthus, aspirated from the center of each eye, pooled in the same syringe and mixed together. After collection, vitreous samples were immediately centrifuged at 3000 *g* for 15 min. The separated supernatant was collected and stored in preservative-free tubes. No specimens were excluded due to insufficient sample volume. All samples were transferred to the laboratories immediately post-collection. When analyses were delayed, samples were stored at −20 °C.

Undiluted cerebrospinal fluid samples (between 1 and 5 ml) were collected by aspiration using a sterile needle and a syringe through a suboccipital puncture. The samples were immediately centrifuged after collection at 3000 *g* for 15 min. The separated supernatant was collected and stored in preservative-free tubes at −20 °C.

Undiluted urine samples (between 5 and 10 ml) were collected by bladder aspiration during autopsy and stored in preservative-free tubes. When analyses were delayed, samples were stored at −20 °C.

Undiluted pericardial fluid samples (between 5 and 10 ml) were collected immediately after pericardium incision during autopsy. Pericardial fluid was immediately centrifuged post-collection at 3000 *g* for 15 min. The separated supernatant was then collected and stored in preservative-free tubes at −20 °C.

Femoral blood samples were collected by aspiration with a sterile needle and a syringe from the femoral vein(s) during autopsy. Blood samples were drawn after clamping the vein(s) at the proximal end and lifting the lower limb(s) for several minutes. Blood was stored in tubes containing sodium fluoride and tubes containing ethylenediaminetetraacetic acid (EDTA). Femoral blood samples were also collected in tubes without preservatives and centrifuged immediately post-collection at 3000 *g* for 15 min. After centrifugation, the separated supernatant (postmortem serum) was collected and stored in preservative-free tube. When analyses were delayed, postmortem serum samples were stored at −20 °C.

Cardiac blood samples were collected after incision of the external sides of the left and right atria during autopsy. Blood was stored in tubes containing sodium fluoride and tubes containing EDTA. When analyses were delayed, samples were stored at −20 °C.

2.3. Systematic laboratory assays

Vitreous glucose, sodium and chloride, postmortem serum urea and creatinine as well as femoral (or cardiac) blood and vitreous 3HB determinations were performed in all cases included in the study.

Sodium, chloride and vitreous glucose were determined on a Dimension® Xpand® Plus Integrated Chemistry System (Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA).

3HB concentrations were determined on a Cobas Mira Plus (Roche Diagnostics, Switzerland) by an enzymatic photometric

method adapted in house from the technique described by Ruell and Gass.[8] Refrigerated or frozen femoral (or cardiac) blood samples as well as refrigerated or frozen vitreous samples were thawed overnight at 4 °C and deproteinized with perchloric acid. Supernatant was used for analysis.

Creatinine (Jaffé method, rate-blanked and compensated) and urea nitrogen (kinetic enzymatic UV assay for urea/urea nitrogen) were determined in postmortem serum from femoral blood with the Roche standard methods on the Roche Modular P-system (Roche Diagnostics GmbH, Mannheim, Germany).

2.4. Additional laboratory assays

Depending on the availability of other biological fluids (urine, pericardial and cerebrospinal fluids) during autopsy and the results of systematic biochemical analyses, additional biochemical investigations were performed in those cases presenting higher vitreous glucose as well as higher blood and vitreous 3HB levels. These analyses included:

- 3HB levels determination in urine, pericardial and cerebrospinal fluids in order to obtain information pertaining to the duration of the death process,
- C-reactive protein (CRP) determination in postmortem serum from femoral blood, in agreement with the observations of Lindroos-Jokinen et al.[9] concerning the increased CRP levels in fatal DKA cases without any other obvious underlying causes, such as infection or trauma,
- glycated hemoglobin determination, in order to assess the glycemic control in the weeks prior to death.

CRP was measured by the commercially available immunoturbidometric assay on the Roche Modular P-system (Roche Diagnostics, Mannheim, Germany). Results were expressed in mg/l. The analytical sensitivity was 0.15 mg/l, according to manufacturer information. Based on laboratory references in living people, CRP values were dichotomized into “normal values” (concentrations lower than 10 mg/l) and “increased values” (concentrations greater than 10 mg/l).

Glycated hemoglobin was determined on whole femoral blood samples stored in tubes containing EDTA by ion-exchange high-performance liquid chromatography (HPLC) (Bio-Rad D-10 Dual Program, Hercules, CA, USA).

2.5. Ethical considerations

All cases selected for this study underwent medico-legal autopsies requested by the public prosecutor. Biochemical investigations were performed as part of medico-legal investigations and no further ethical permission was required to perform laboratory analyses.

3. Results

Based on death scene appearances, radiological images, autopsy data, histological and neuropathological findings as well as toxicology results, six groups of medico-legal situations (corresponding to 206 autopsy cases), possibly causing either prolonged loss of consciousness or death were identified:

- acute coronary artery thrombosis (macroscopically and microscopically appearing as ruptured plaques with superimposed occlusive or partially occlusive thrombosis), without cardiac rupture (21 cases),
- acute myocardial infarction without cardiac rupture (8 cases),
- head injury (in most cases, falls at home involving stairs) characterized by severe cerebral edema, associated with other damage such as skull fractures, acute epidural hematoma, subdural hemorrhage, subarachnoid hemorrhage, intraparenchymal hemorrhage or brain contusion(s) (26 cases),
- subarachnoid or intraparenchymal hemorrhage following cerebral aneurysm or vascular malformation rupture (4 cases),
- massive gastro-intestinal bleeding following ulcers, inflammatory diseases, hemorrhagic disorders, polyps and tumors, without concomitant hepatic cirrhosis, hepatic insufficiency or esophageal varices (6 cases),
- presence of psychotropic drug(s) in blood at lethal levels (141 cases) as defined by the literature.[10,11]

Markedly increased vitreous glucose concentrations were defined as higher than 10 mmol/l (180 mg/dl), blood 3HB concentrations leading to potentially fatal DKA were defined as higher than 2.5 mmol/l (26 mg/dl) and vitreous 3HB concentrations leading to potentially fatal DKA were defined as higher than 6 mmol/l (63 mg/dl), in agreement with the reference standards suggested by Iten and Meier,[12] Zilg,[13] Palmiere[14] and Heninger.[15]

In 3 out of 206 cases (1 male and 2 females), postmortem biochemical investigations revealed pathologically increased vitreous glucose as well as blood and vitreous 3HB levels, the latter potentially explaining in themselves the death through the onset of DKA. Sodium, chloride, urea and creatinine were at normal levels in all these three cases. Complementary biochemical investigations confirmed the presence of pathologically higher 3HB levels in all analyzed biological fluids (urine, pericardial and cerebrospinal fluids), glycated hemoglobin at normal levels and CRP concentrations at higher than normal levels.

Case number 1 concerns a 40-year-old alcoholic woman who had been suffering from type 2 diabetes mellitus treated with metformin. As stated in the medical records, she also suffered from hypertension and recurrent pancreatitis. She was found dead in her apartment in the evening. As reported by witnesses, the day prior to her death she had a violent quarrel with her boyfriend. They physically fought and exchanged blows. She fell to the ground and hit her head on the floor. She did not complain of any pain, headache or other neurological symptoms. However, on the day she died, the victim stayed in bed all day.

Unenhanced CT-scan, autopsy and neuropathology revealed the presence of a large, acute, left-sided subdural hemorrhage surrounding the left cerebral hemisphere, with mass effect on the left cerebral hemisphere and left lateral ventricle as well as displacement of the left hemisphere beyond the midline. Cerebral edema with left uncal herniation was also observed. Toxicological analyses revealed the presence of tramadol and oxazepam in blood, both within therapeutic ranges.

Tramadol was also detected in urine. Histology and immunohistochemistry of the pancreas revealed diffuse atrophy of the islets of Langerhans without signs of hemorrhage or inflammation.

Case number 2 concerns a 47-year-old alcoholic woman with type 1 diabetes treated with insulin. According to medical records, she also suffered from essential hypertension for which several medications, including a beta-blocker and an angiotensin-converting enzyme (ACE) inhibitor, were prescribed. Furthermore, hyperlipidemia was treated with simvastatin, bipolar disorder with olanzapine and anxiety with oxazepam. She was found dead in her apartment in the afternoon.

She was described by her physician as a non-compliant patient pertaining both to medical instructions and treatment, especially concerning benzodiazepine intake without or against medical advice.

Unenhanced CT-scan and autopsy failed to reveal the cause of death. Toxicological analyses revealed the presence of flurazepam,

desalkylflurazepam, temazepam and oxazepam in blood, the concentrations of which were increased though still fell within therapeutic levels. Neither olanzapine nor its metabolites were identified in blood or urine. Histology and immunohistochemistry of the pancreas showed a significant atrophy of the islets of Langerhans without inflammatory cell infiltration or hemorrhage.

Case number 3 concerns a 32-year-old male substance-abuser, with type 1 diabetes treated with insulin. According to medical records, he also suffered from a psychiatric disorder for which he received olanzapine and lorazepam. He was described by his physician (endocrinology specialist) as non-compliant regarding both medical instructions and treatment. Unenhanced CT-scan, autopsy and histology revealed large amounts of fresh and brownish, digested blood in the stomach, duodenum and jejunum, aspiration of fresh and digested blood in the upper and lower airways as well as multiple gastric erosions with gastritis. Toxicological analyses revealed the presence of lorazepam and benzoylecgonine in blood. In urine, benzoylecgonine, methylecgonine, lorazepam and diclofenac were also identified, the latter suggesting the possibility of a nonsteroidal anti-inflammatory drug (NSAID)-induced gastric bleeding. The presence of cocaine and its metabolites in urine and their absence in blood indicated a non-recent use of this substance, probably going back to several hours before death. Blood concentration of lorazepam was in the potentially lethal range. Neither olanzapine nor its metabolites were identified in blood or urine. Histology and immunohistochemistry of the pancreas showed significant atrophy of the islets of Langerhans without inflammatory cell infiltration, normal glucagon immunoreactivity and almost a complete absence of insulin immunoreactivity.

Complete biochemical results concerning these three cases are reported in Table 1. Interestingly, glycated hemoglobin concentration was not increased in any of these cases. This was a relatively surprising observation considering that case numbers 2 and 3 had been described as non-compliant patients regarding both medical instructions and treatment. Glycated hemoglobin has been described as a stable laboratory parameter for at least 36 h after death. Moreover, no significant changes have been observed in blood concentration levels after 40 h of sample storage at 4 °C.[16,17] Though autopsies of the three mentioned cases had been performed within 30 h after body discovery, a longer interval had elapsed between death and blood sampling that might have influenced glycated hemoglobin postmortem stability and therefore subsequent result analysis.

4. Discussion

The two most common precipitating factors in the development of DKA are inadequate or inappropriate insulin therapy and infection, though alcohol consumption and drug use have been reported as capable of precipitating ketoacidosis in patients with diabetes. This may be due either to the substance's direct effect on carbohydrate metabolism and subsequent worsening of hyperglycemia or through other mechanisms, such as instigating poor compliance with insulin therapy.[3,4,6,7]

The postmortem diagnosis of DKA is currently based on the identification of some specific biochemical parameters that are mainly represented by pathologically increased vitreous glucose and blood ketone (acetone and/or 3HB) levels. Increased ketone levels in vitreous and pericardial fluid are also thought to reliably indicate the presence of DKA at the time of death. Further biochemical analyses, such as glycated hemoglobin determination or glucose measurement in urine, may provide additional data to assess glycemic control during the weeks preceding death or confirm hyperglycemia at the time of death. However, these latter findings do not allow the diagnosis of DKA to be established in and among themselves.

If, on the one hand, available medical records documenting a history of diabetes mellitus are significant, several reports, on the other, were published in medico-legal literature concerning the postmortem diagnosis of DKA in subjects with unsuspected and undiagnosed diabetes mellitus.[18–23]

In addition to these cases of "unexpected" DKA diagnosis that highlight the usefulness of systematic biochemical investigations in forensic pathology routine, other relatively frequent situations of forensic interest deserve to be systematically explored and carefully considered, so as to avoid misdiagnosis. Indeed, these cases pertain to all those conditions of unintentional therapeutic errors, involving either insulin or hypoglycemic agents, which are caused by changes in mental status possibly incapacitating individuals, making them unable to obtain help or take actions to prevent metabolic and potentially fatal disorders from arising.

Moreover, since confusion, unconsciousness or coma may be manifestations of coexisting disorders that can lead to death on their own (including coronary artery thrombosis, myocardial infarction, cerebral edema, intracranial or intraparenchymal hemorrhage, brain contusion, gastro-intestinal bleeding as well as lethal or potentially lethal drug concentrations in blood), the ability to

Table 1
Summarizes the main results of postmortem biochemical investigations observed in the three potentially fatal ketoacidosis cases described in the text.

Case	Age	Gender, height, weight	Glycated hemoglobin	VH glucose	VH sodium	VH chloride	Blood 3HB	VH 3HB	PF 3HB	Urine 3HB	CSF 3HB	Serum CRP
1	40	F 165 cm 69 kg BMI 25.3	5.8% (40 mmol/mol)	33 mmol/l (595 mg/l)	148 mmol/l (148 mEq/l)	124 mmol/l (124 mEq/l)	7 mmol/l (73 mg/dl)	7 mmol/l (73 mg/dl)	8 mmol/l (83 mg/dl)	12 mmol/l (125 mg/dl)	5 mmol/l (52 mg/dl)	81 mg/l
2	47	F 170 cm 62 kg BMI 21.5	6.6% (49 mmol/mol)	41 mmol/l (739 mg/l)	135 mmol/l (135 mEq/l)	103 mmol/l (103 mEq/l)	21 mmol/l (219 mg/dl)	16 mmol/l (167 mg/dl)	20 mmol/l (208 mg/dl)	31 mmol/l (323 mg/dl)	8 mmol/l (83 mg/dl)	75 mg/l
3	32	M 178 cm 65 kg BMI 20.5	5.6% (38 mmol/mol)	32 mmol/l (577 mg/l)	141 mmol/l (141 mEq/l)	112 mmol/l 112 mEq/l)	16 mmol/l (167 mg/dl)	14 mmol/l (146 mg/dl)	16 mmol/l (167 mg/dl)	27 mmol/l (281 mg/dl)	11 mmol/l (115 mg/dl)	90 mg/l

VH = vitreous humor.
3HB = 3-beta-hydroxybutyrate.
PF = pericardial fluid.
Serum = postmortem serum.

distinguish the ultimate cause of death (the metabolic disorder) from other underlying diseases potentially causing death themselves or incapacitating individuals long enough for a hyperglycemic state to develop, becomes decisive.

Few reports are available in medico-legal literature describing diabetic ketoacidosis found in conjunction with other conditions either incapacitating or potentially leading to death on their own.

Byard et al.[24] reported two cases of death in insulin-requiring diabetics, a 45-year-old woman and a 27-year-old man. Both presented pathologically increased vitreous glucose and 3HB levels associated with potentially lethal drug concentrations in blood. Both individuals were found dead with no organic diseases or injuries identified at autopsy that could have caused death. Further similarities included a common clinical history of diabetes mellitus and prescription drug use. In the first case, toxicological screenings and biochemical investigations showed a lethal level of sertraline and a potentially lethal level of methadone. The second case also revealed a potentially lethal level of methadone, along with established lethal DKA in both situations. Even though the precise cause of death was difficult to determine in these cases due to evidence of both established lethal DKA and potentially lethal drug levels, the authors concluded that drug toxicity, along with DKA, played a role in the terminal events, with sedation from drugs causing incapacitation or unconsciousness long enough for ketoacidosis to occur. The authors also postulated that the two subjects had likely been affected by drugs prior to their deaths and that drug intoxication had likely impaired their ability to administer insulin, resulting in the development of diabetic ketoacidotic states over time.

Whereas the relationship between diabetes mellitus, ketoacidosis and second-generation antipsychotics has frequently been discussed in psychiatric and medico-legal literature, few reports have focused on the relationship between drug use, especially recreational, and acute complications of diabetes mellitus, save perhaps cocaine.[5,25,26] Fatal DKA may be the initial presentation of diabetes in some patients receiving antipsychotic medications and some of these deaths may fall under the purview of the inquiring authorities and forensic pathologists due to their precipitous, out-of-hospital circumstances.[25,26]

Numerous recreational drugs are known as being able to influence glucose and insulin metabolism, suggesting that their use can theoretically be responsible for death either through hyperglycemia and ketoacidosis in diabetics or through heart or respiratory failure in non-diabetic users. Amphetamines have a counter-regulatory action to insulin via 5-hydroxytryptamine-stimulated catecholamine release. Ecstasy promotes a massive release of serotonin from the presynaptic cleft and inhibits serotonin reuptake. This substance is also a potent dopamine and norepinephrine releasing agent that creates a syndrome of inappropriate antidiuretic hormone release. In the context of excessive water consumption, this places diabetic individuals in double jeopardy with the risk of DKA and cerebral edema secondary to hyponatremia. Cocaine is a powerful sympathomimetic drug that has potent effects on counter-regulatory hormone concentrations. In animal studies, cocaine increases catecholamine levels by stimulating the adrenal medulla to release epinephrine and norepinephrine. Individuals intoxicated by cocaine also have elevated epinephrine and norepinephrine levels. Other studies have described increased concentrations of corticotropin and cortisol in human subjects following cocaine administration. Hence, stimulation of either catecholamine release or the hypothalamic-pituitary-adrenal axis by cocaine use might act as a precipitating factor in DKA.[7,27,28]

Umpierrez et al.[6] and Warner et al.[7] observed that cocaine use was found in a significant number of adults admitted to hospital with DKA and was associated with more frequent omission of insulin therapy as well as the absence of precipitating systemic illnesses. Although poor compliance with insulin therapy was the most common precipitating cause of ketoacidosis in diabetic cocaine users, Warner et al.[7] postulated that the action of cocaine on counter-regulatory hormone release in itself could contribute to the development of ketoacidosis even in the absence of underlying systemic illnesses. Irrespective of the mechanism promoting ketoacidosis, the results of the mentioned studies should encourage clinicians caring for diabetic patients, either using recreational drugs or treated with second-generation antipsychotic medication, to emphasize the risks of fatal ketoacidosis related to insulin therapy omission or medical treatment metabolic side effects.

In the cases herein described we identified two situations. One in which DKA coexisted with underlying features potentially incapacitating or leading to death themselves (subdural hemorrhage and cerebral edema in case number 1, massive gastric bleeding and aspiration of blood in the airways in case number 3), the other in which it corresponded to increased, potentially lethal or lethal concentrations of drugs (cases 2 and 3).

Moreover, in case number 3 the presence of cocaine and its metabolites in urine and their absence in blood indicated a non-recent use of this substance, probably several hours before death, which could also have played a role in disrupting metabolic homeostasis and glycemic control.

In all the above cases, biochemical investigations revealed pathologically increased and comparable 3HB concentrations in blood, vitreous, pericardial and cerebrospinal fluids. Assuming that the equilibrium between blood and other body compartment fluids (vitreous, pericardial and cerebrospinal fluids) is established over time, these findings may additionally suggest that ketoacidosis and the death process developed over several hours. Additionally, these results can support the hypothesis that subdural hemorrhage, gastric bleeding, blood aspiration and drug intoxications, namely the “incapacitating states”, did not cause the death themselves in a short interval of time but rather impaired the ability of the subjects to take their medication, with the final result of DKA development over time.

Lastly, the cases herein presented emphasize the usefulness of performing postmortem biochemical investigations in biological fluids beyond blood and vitreous systematically. This should be done in order to identify DKA-related deaths not only in sudden unexpected deaths with negative autopsies and a history of second-generation antipsychotic treatment or cocaine use, but even when autopsy and toxicology results provide apparently conclusive findings. Indeed, the mechanism of death can sometimes be more complex than simple “drug toxicity” or “diabetic ketoacidosis” and may occasionally require considering more than one possible cause of death in cases that might have initially appeared relatively straightforward.

Conflict of interest

The authors have no conflict of interest to declare. They have no controlling interests in the Journal of Forensic and Legal Medicine.

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Ethical approval

None.

All cases selected for this study underwent medico-legal autopsies requested by the public prosecutor. Biochemical investigations were performed as part of medico-legal investigations and no further ethical permission was required to perform laboratory analyses.

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